CHD7 in Charge of Neurogenesis

Kimberly H. Kim[1,2,3] and Charles W.M. Roberts[1,2,3,*]
[1]Department of Pediatric Oncology, Dana-Farber Cancer Institute, Boston, MA 02215, USA
[2]Division of Hematology/Oncology, Boston Children's Hospital, Boston, MA 02115, USA
[3]Department of Pediatrics, Harvard Medical School, Boston, MA 02115, USA
*Correspondence: charles_roberts@dfci.harvard.edu
http://dx.doi.org/10.1016/j.stem.2013.06.010

In this issue of *Cell Stem Cell*, Feng et al. (2013) report that the gene mutated in human CHARGE syndrome, ATP-dependent chromatin remodeling factor CHD7, contributes to the control of neurogenesis. The authors also report that exercise ameliorates these defects and suggest it as an intervention worthy of study in CHARGE syndrome.

Progressive compaction of DNA wrapped around histone octamers to form nucleosomes and higher-order chromatin structures constitutes an organizational mechanism for DNA storage. However, this compaction also presents barriers to gene expression because the transcriptional machinery requires access to DNA. Consequently, dynamic modulation of DNA accessibility by chromatin remodeling complexes is an important mechanism for controlling cell fate during development and, when deregulated, causing disease. In this issue of *Cell Stem Cell,* Feng et al. (2013) seek to characterize the contributions of CHD7, an ATP-dependent chromatin remodeler, to developmental and adult neurogenesis.

Chromatin modifiers can be organized into two classes that contribute to transcriptional regulation, those that covalently modify histones and those that utilize the energy of ATP hydrolysis to mobilize nucleosomes and remodel chromatin structure. Mutations in genes encoding chromatin remodelers are increasingly recognized as frequently occurring in cancer (Wilson and Roberts, 2011), but they are also linked with developmental disorders. Some of these include *ERCC6* in cerebro-oculo-facio-skeletal syndrome, *ATRX* in ATRX-syndrome and α-thalassemia myelodyspasia syndrome, genes encoding subunits of the SWI/SNF (BAF) chromatin remodeling complex in Coffin-Siris syndrome (Tsurusaki et al., 2012), and *CHD7* in CHARGE syndrome (Clapier and Cairns, 2009). The CHD (chromodomain-helicase-DNA-binding protein) family is a subclass of ATP-dependent remodelers. De novo heterozygous mutations of CHD7 are the principal cause of the complex developmental disorder CHARGE syndrome, characterized, in addition to other anomalies, by olfactory defects and mental retardation (Bergman et al., 2011). Homozygous inactivation of *Chd7* in mice results in embryonic lethality at day E10.5 while heterozygous mutations produce phenotypes similar to human CHARGE, including postnatal growth delay, vestibular dysfunction, and olfactory defects (Bosman et al., 2005; Hurd et al., 2007). However, the mechanisms by which mutation of this chromatin remodeler result in specific developmental defects are poorly understood.

In this issue of *Cell Stem Cell,* Feng et al. (2013) investigate how CHD7 contributes to regulation of adult neurogenesis. They show that CHD7 expression is highly enriched in the subventricular zone and subgranular zone (SVZ and SGZ), two neurogenic areas of the mammalian brain. They demonstrate that CHD7 expression, although not present in quiescent neural stem cells (NSCs), increases in active NSCs, peaks in transit-amplifying progenitors, and persist in neuroblasts. The authors next inactivate Chd7 in Tlx- or Nestin-expressing neural stem cells (NSCs) using Chd7 conditional mice and find that deletion of CHD7 leads to decrease of both SVZ and hippocampal neurogenesis. Loss of CHD7 is shown to have no effect upon NSC self-renewal but instead blocks differentiation, thus inhibiting neurogenesis. Consequently, CHD7 is dispensable for the maintenance of NSC populations, but essential for differentiation into neural populations. Notably, the authors find that voluntary running is able to rescue the reduced hippocampal neurogenesis of the CHD7 mutant mice.

To investigate the mechanistic basis for the contributions of CHD7 to NSC differentiation, the authors searched for genes whose expression most parallels that of CHD7 itself, reasoning that such genes may be enriched for direct targets of this chromatin remodeler. Using The Cancer Genome Atlas (TCGA), two transcription factors essential for neuronal identity, Sox4 and Sox11, were identified as most highly correlated with CHD7 expression. The promoters of these genes were then identified as bound by CHD7. The authors also show that these genes are activated via CHD7 contributions to decompaction of nucleosomes at their promoters. A central role for Sox4 and Sox11 is suggested by the finding that forced expression of these genes circumvents the differentiation blockade resulting from CHD7 loss.

Collectively, the work of Feng et al. identify CHD7 as a regulator of neurogenesis that directly controls the acquisition of neural fate by regulating expression of transcription factors Sox4 and Sox11 (Figure 1). Given that chromatin remodeling factors are typically capable of interacting with many regulatory proteins (Batsukh et al., 2010), it will be of interest to determine how CHD7 is targeted to Sox4 and Sox11 promoters and whether it contributes to other aspects of chromatin structure at these targets.

Perhaps one of the most provocative findings by Feng et al. is the amelioration of the CHD7 loss phenotype brought about by physical exercise. Exercise has been shown to have stimulatory effects upon neurotransmitters and to increase survival of nascent neurons in

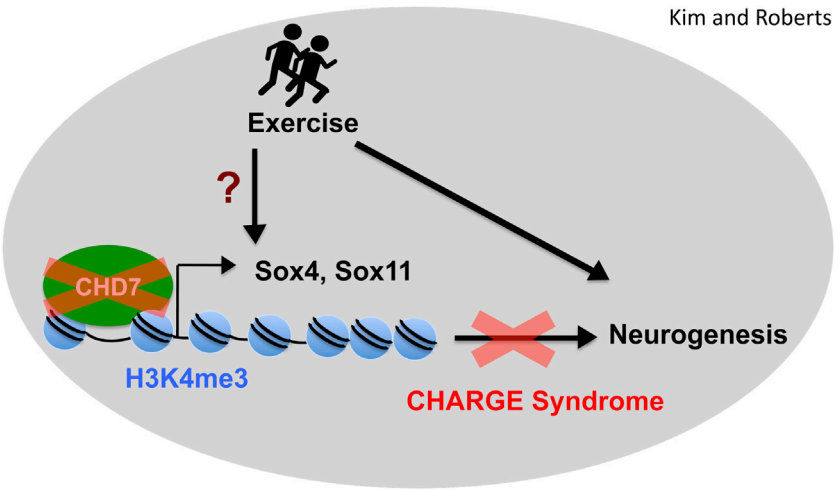

Figure 1. CHD7 and Physical Exercise in CHARGE Syndrome
CHD7 functions as a regulator of neurogenesis via direct binding to the promoters of fate-controlling transcription factors to facilitate open chromatin structure. Feng et al. show that exercise may ameliorate the neurogenic defects otherwise caused by CHD7 mutation.

the SGZ zone in Parkinson's disease models (Frazzitta et al., 2013), a zone in which neurogenesis is impaired following CHD7 loss. Via the provision of an exercise wheel, the authors therefore examine the effects of voluntary running upon the number of neurons and dendrite development, both of which are negatively affected by CHD7 mutation. Strikingly, they report that exercise results in improvement of both phenotypes. While the CHD7 findings could raise the possibility of exercise being used as a therapy for patients with CHARGE syndrome, the findings by Feng et al. must be considered preliminary until they can be tested for reproducibility. Nonetheless, further investigation in mouse models should be pursued and, if confirmed, may warrant consideration of human studies. It should be kept in mind that the phenotypic changes characterized here arose from targeted knockout of CHD7 in a mature NSC population. It will be of interest to determine whether similar interactions occur in other tissues affected in CHARGE syndrome and also how CHD7 interacts with other chromatin modifiers and transcription factors to regulate transcription. Gaining a deeper understanding of the molecular function of CHD7 should provide insight into CHARGE syndrome, and perhaps other chromatin-based diseases, and may offer clues for novel approaches to therapy.

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